

***RESIDENT RESEARCH PROPOSAL TEMPLATES:
7/16/2015***

**Effect of bupivacaine-infused fibrin sealant
application on post-tonsillectomy pain &
hemorrhage: A clinical trial**

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Clinicaltrials.gov # NCT02343263

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Otolaryngology – Head & Neck Surgery (Official Journal of the American Academy of Otolaryngology-Head & Neck Surgery)

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Study Schema

1.0 Background:

A History of Tonsillectomy Surgical Technique

The effort by surgeons to reduce post-tonsillectomy hemorrhage and pain is as ancient as the procedure itself. Blunt digital tonsillectomy was first described in detail by Roman physician Aulus Cornelius Celsus who operated in Rome in the first century B.C. (McNeill, Júnior). The Greek physician and philosopher Galen of Pergamon later described a snare technique for tonsil amputation in the late 2nd century A.D. which was presumably the most common technique in use at that time (McNeill). In the late 5th century A.D., the Byzantine Aëtius of Amida first advocated partial tonsillectomy by removing only the exophytic visible tonsil tissue; this method protected the more robust hemorrhage-prone vasculature deep to the tonsil capsule and reduced pain-inducing injury to the peritonsillar musculature (McNeill, Júnior). Two centuries later, another Byzantine physician known as Paulus of Aegina recommended complete tonsillectomy with hook and curved scalpel while warning against operating on acutely inflamed tonsils in order to reduce hemorrhage risk. Further refinements in tonsillectomy technique were developed over the subsequent centuries (McNeill).

By the dawn of the 1700s, the Scottish physician Peter Lowe described only three techniques then in use: the snare, the ligature, and the excision; but all three were associated with varying degrees of postoperative pain and hemorrhage risk (McNeill). The first guillotine tonsillotome was developed as an alteration of the then centuries-old uvulotome in the late 1820s by Philip Physick, an American surgeon who trained in Philadelphia and abroad in Scotland; this instrument purportedly offered reduced postoperative pain as well as reduced hemorrhage risk compared to prior methods (McNeill, Júnior). The guillotine tonsillotome underwent modifications by Physick himself and later by William Fahnestock in the early 1800s (Júnior).

Guillotine tonsillotome dissection remained the mainstay of surgical approaches during the early part of the nineteenth century (McNeill). However, the surgical experiences and reports of American surgeons W. L. Ballenger and later Greenfield Sluder as well as British surgeons George Waugh, Samuel Whillis and Frederick Pybus cumulatively led to a return of complete tonsillectomy as the standard of care (McNeill, Júnior). With the development of modern anesthesia, intubation techniques, and the specialty field of Otorhinolaryngology, more rapid progress in reducing post-tonsillectomy pain and hemorrhage were developed (Júnior). An emphasis on utilizing cold steel with forceps and scalpels was reported to produce less intraoperative and postoperative bleeding. General anesthesia allowed Dr. Lee Cohen to develop and promote routine peritonsillar vessel ligation for prevention of postoperative tonsil hemorrhage in 1910 (Júnior, Cohen L). This hemostatic development was subsequently followed in the 1930s by Dr. Gregg Dillinger's use of electrical diathermy to cauterize the wound bed during complete tonsillectomy and thereby reduce postoperative hemorrhage although this thermal injury increased postoperative pain (Júnior).

By the 1940s, tonsillectomy had become the most frequently performed surgical procedure in the United States with nearly two million performed annually for a variety of appropriate and questionable indications (Júnior, Myers). Reports indicate that

procedure requests by patients because of the publicity of a famous person having undergone tonsillectomy were not uncommon (McNeill). Despite the popularity and incidence of tonsillectomy at that time, the problem of postoperative pain and hemorrhage remained. Monopolar cautery, which had been previously invented for other surgical approaches, was adapted and became the mainstay approach to tonsillectomy in the following years in the United States (Myers).

The last several decades, has seen an increasing prevalence of American otolaryngologists (Ear, Nose & Throat physicians or ENTs) favoring electrocautery techniques and a concomitant proliferation of such techniques. Approximately 50% of ENTs now utilize monopolar cautery handheld instruments (Myers). A smaller but growing proportion of surgeons are using coblation electrosurgery which utilizes bipolar electrical current to induce a plasma field capable of dissecting tissue at temperatures much lower than that of monopolar cautery (Myers). In fact, coblation temperatures range from 40° Celsius (C) to 70°C while monopolar cautery temperatures are known to exceed 400°C (Walner). Coblation offers similar or less postoperative pain compared to monopolar cautery, similar postoperative hemorrhage rates, and the ability to perform concurrent adenoidectomy with a single instrument as well (Myers). Less than 10% of surgeons in the United States continue to use cold steel sharp dissection with vessel ligation for hemostasis (Myers, Walner). A variety of other modern but less commonly performed techniques exist which include laser ablation, radiofrequency ablation, harmonic scalpel excision, and partial/intracapsular tonsillectomy with powered instruments (Myers).

History of Perioperative Interventions to Reduce Post-Tonsillectomy Pain & Hemorrhage

While the surgical technique for tonsillectomy has progressed dramatically in the last two millennia, adjunctive medicinal efforts to improve post-tonsillectomy pain and hemorrhage have also improved. Celsus (1st century B.C.) recommended milk and vinegar styptic application for perioperative hemorrhage while acknowledging the discomfort of acid application to the tonsil fossae (McNeill, Júnior). Paulus of Aegina (7th century) recommended prophylactic cold water or oxycrate rinses, but in the case of active hemorrhage prescribed rinsing with water containing essence of boiled brambles, rose, or myrtles leaves (McNeill). British pioneer of laryngology Morrell MacKenzie (19th century) described use of tanno-gallic acid application for control of post-tonsillectomy hemorrhage as well as the utility of marshmallow consumption on postoperative pain control (McNeill). Later in the 19th century, Dr. Jacob Cohen in his book, "Diseases of the Throat" described the use of persulfate of iron to control postoperative tonsil bleeding (Cohen, JS).

More recent common medicinal adjuncts including perioperative systemic steroid use, perioperative antibiotics, scheduled postoperative oral pain medication regimens, intraoperative local anesthetic injection, and intraoperative topical anesthetic usage have been evaluated as well. The 2011 Clinical Practice Guidelines for Tonsillectomy in Children produced by the American Academy of Otolaryngology – Head & Neck Surgery strongly recommended the administration of a single intraoperative dose of intravenous dexamethasone which has been shown to significantly decrease postoperative emesis as well as pain (Baugh). The same source strongly recommended a well-articulated parent-friendly weight-based pain control regimen including acetaminophen with or without

narcotic and non-steroidal anti-inflammatory medications such as ibuprofen (Baugh). The Guidelines strongly recommended against routine perioperative antibiotic use for lack of evidence demonstrating benefit and the frequency of adverse events (Baugh).

A 1999 Cochrane Systematic Review evaluated the literature at that time supporting the routine use of local anesthetic injection and the 5 studies which met inclusion criteria demonstrated no clear benefit in postoperative pain control based on what the reviewers felt were appropriate pain assessment tools (Hollis). The same review article analyzed a single study which evaluated the efficacy of topical anesthetic spray and also found a lack of appropriate data to support sustained improvement in postoperative pain control (Hollis). The lack of efficacy for local anesthetic use is likely secondary to the fact that postoperative pain continues for a week or more after the surgery and local anesthetics are likely cleared from sites and metabolized within a day (Hollis).

Tonsillectomy and adenotonsillectomy remain among the most frequently performed ambulatory pediatric surgeries in the United States with common indications for this surgery in adults and children including chronic tonsillitis and obstructive sleep apnea. Less common indications for these surgeries include peritonsillar abscesses, tonsillar asymmetry, and concern for malignancy (Myers). Yet despite the great progress in surgical and medicinal techniques, post-tonsillectomy pain and hemorrhage continue to be not infrequent complications. Pediatric patients are particularly prone to inadequate postoperative pain control which often leads to a downward spiral of worsening pain, decreasing oral tolerance, refusal of pain medications, and ultimately dehydration prompting emergency room evaluation. Hemorrhage rates remain between 1 and 7% in the United States and similarly prompt emergency room visits, readmissions, and return trips to the operating room for hemorrhage control (Myers). Addressing post-tonsillectomy pain and hemorrhage continue to be one of the most frequent and troublesome issues facing the otolaryngologist on call overnight.

Therefore great incentive and potential benefit exists, for both patients and surgeons, to continue research efforts toward further ameliorating post-tonsillectomy pain and hemorrhage. Despite the 1999 Cochrane Systematic Review's recommendation against use of injection and topical local anesthetics, researchers have continued to analyze the relative effect of different local anesthetics on postoperative tonsillectomy pain. The most commonly studied local anesthetics include lidocaine and bupivacaine, the latter known for its greater potency and longer half-life.

Kaygusuz in 2003 compared topical dexamethasone, topical bupivacaine, and topical lidocaine to each other and against placebo and determined that all medications were superior to placebo in reducing postoperative pain during the first week after pediatric tonsillectomy, with lidocaine scores superior to bupivacaine only on postoperative day 3 (Kaygusuz). In 2011, Ozmen & Ozmen compared topical lidocaine with epinephrine to topical bupivacaine administration in a randomized controlled trial of 60 patients and found that while both anesthetics were superior to saline placebo, the topical bupivacaine remained superior to lidocaine from postoperative hour 17 through postoperative day 4 (Ozmen). A meta-analysis performed by Sun et al. included 7 studies comparing bupivacaine injection to saline placebo and found that bupivacaine injection significantly reduced postoperative analgesia requirements and improved postoperative pain control (Sun). More recently in 2014, Haksever et al. compared injection bupivacaine to topical bupivacaine in pediatric patients and found that topical bupivacaine was superior in reducing postoperative pain than injection bupivacaine from

the 5th postoperative hour up to the 5th postoperative day (Haksever). Cumulatively these more recent studies call into question the findings of the older Cochrane Review and suggest the superiority of topical bupivacaine over topical lidocaine, injection lidocaine, or injection bupivacaine in reducing postoperative tonsillectomy pain.

Another adjunctive medical treatment which has been explored in recent literature is the application of the hemostatic fibrin sealant to the tonsil fossae following tonsillectomy. Fibrin sealants utilize clotting factors to imitate the natural coagulation process and have been utilized in a wide variety of applications across surgical specialties (Dhillon). Several brand name fibrin sealants exist, but each has similar pharmacodynamics which involve mixing a solution of fibrinogen/anti-fibrinolytic with a solution of thrombin/calcium-chloride to produce a cross-linked protein matrix which demonstrates both hemostatic, adhesive, and porous properties (Dhillon, Spicer). Over time, the fibrin sealant is lysed slowly by endogenous enzymes in the patient's tissues and absorbed (Dhillon). Stiller-Timor et al. analyzed the serum of patients who had fibrin sealant applied to the tonsil fossae following tonsillectomy and determined there was a significant reduction in the postoperative elevation of serum inflammatory cytokines and neutrophils immediately postoperatively and 12 hours postoperatively compared to patients who did not receive fibrin sealant; this suggests topical fibrin sealant may blunt the postoperative systemic inflammatory response (Stiller-Timor).

Moralee et al. first evaluated use of fibrin sealant application to the tonsil fossae in 1994 and found that its use resulted in less postoperative pain than diathermy hemostasis (Moralee). In 1999, Stoeckli et al. reported a small study comparing bipolar electrocautery alone for hemostasis on one tonsil fossa versus bipolar electrocautery followed by application of fibrin sealant on the contralateral tonsil fossae within the same patient but found no significant difference between patient self-assessment of which tonsil fossa had more pain nor in hemorrhage rates between sides (Stoeckli). Another small study by Gross et al. in 2001 evaluated the addition of fibrin sealant to blunt dissection tonsillectomy with ligature hemostasis in pediatric patients; they found significant reductions in postoperative pain and emesis on the first postoperative day and a non-significant trend toward less pain the subsequent days (Gross).

Stevens & Stevens in 2005 compared electrocautery alone for hemostasis versus electrocautery with the addition of fibrin sealant in adults and found that the treatment arm was narcotic free 48 hours earlier and more rapidly returned to work and regular activities (Stevens). Three subsequent studies by Vaiman and various colleagues in 2003, 2006, and 2007, also demonstrated that fibrin sealant hemostasis alone resulted in less postoperative adenotonsillectomy pain than electrocautery hemostasis and suggested benefits in preventing postoperative tonsil hemorrhage as well (Vaiman 2003, Vaiman 2006, Vaiman 2007). Jo et al. in 2007 applied Floseal®, a product containing similar hemostatic components to fibrin sealant, to one tonsil fossa and utilized electrocautery alone on the other tonsil fossa and found significantly reduced intraoperative blood loss and operative times as well as significant reductions in pain from postoperative days 2 through 11 and significantly faster returns to normal activity and normal diet (Jo). Segal in 2008 and Nam in 2011, however, found no difference in postoperative pain, analgesic use, or time to return to normal activities or diet when comparing electrocautery hemostasis alone to electrocautery hemostasis followed by fibrin sealant application (Segal, Nam). Park et al. in 2009, in contradistinction to Segal and Nam's studies, reported significantly reduced pain scores on postoperative days 1, 3, and 10 on the tonsil fossa which received fibrin sealant application after

electrocautery hemostasis compared to control tonsil fossae receiving only electrocautery hemostasis without fibrin sealant application (Park).

While the literature offers promising but conflicting evidence of the efficacy of local anesthetics and fibrin sealants, a growing body of literature exists which demonstrates fibrin sealant as an effective drug delivery medium for a variety of clinical applications including delivery of local anesthetics (Spicer, Kitajiri, Zhibo). A large number of in vitro and in vivo studies have explored the use of fibrin sealant in the delivery of growth factors, chemotherapeutic agents, adenoviral gene vectors and synthetic medications (Spicer, Tofuku). An in vitro study by Itokazu in 1996 demonstrated the sustained release of lidocaine from fibrin sealant over 4 days (Itokazu). In 2001, Kitajiri et al. evaluated the application of fibrin sealant mixed with 4% lidocaine to the tonsillectomy wound bed and found that the lidocaine/fibrin sealant mixture significantly reduced the number of days when patients required analgesics and to return to normal diet compared to no sealant use; the fibrin sealant alone group did not achieve significant reductions and no adverse events in any group were noted (Kitajiri). Literature review demonstrates no other reports of using fibrin sealant mixed with topical anesthetic to provide sustained local anesthetic release and postoperative pain control following tonsillectomy or adenotonsillectomy. In 2009, Zhibo & Miaobo utilized a similar technique to significantly reduce postoperative pain following subpectoral breast augmentation by mixing lidocaine with fibrin sealant and applying it to the wound bed whereas lidocaine alone or fibrin sealant alone were significantly less effective (Zhibo). More recently, Haddock et al. in 2014 reported significantly reduced post-anesthesia care unit postoperative pain scores following hand surgery with the combination of lidocaine and bupivacaine with topical thrombin applied to the wound bed before closure compared to patients who received only the topical anesthetics without thrombin (Haddock).

2.0 Rationale, Hypothesis, and Specific Aims / Outcomes

Rationale for this Research

Keeping in mind the ongoing need for improved postoperative tonsillectomy pain management and hemorrhage prevention, as well as the above cited recent advances in the use of fibrin sealant and local anesthetics, it is the purpose of this protocol to evaluate the effects of applying fibrin sealant infused with 0.75% bupivacaine to the tonsil fossae (and adenoid bed, if appropriate) following pediatric and adult tonsillectomy or adenotonsillectomy. The studies above demonstrate the superiority of bupivacaine over lidocaine in the treatment of post-tonsillectomy pain (Ozmen, Sun, Haksever). Bupivacaine offers several general advantages over lidocaine which include greater potency and longer duration of action; both local anesthetics are primarily metabolized by the liver, but the safe maximum dose for bupivacaine without epinephrine injection is lower at 2.5mg/kg compared to 5mg/kg allowed for lidocaine without epinephrine (Lerman).

Hypothesis

We hypothesize that children undergoing tonsillectomy or adenotonsillectomy followed by application of bupivacaine-infused fibrin sealant to the tonsil fossae (and

adenoid bed, if appropriate) will experience less postoperative pain as determined by validated pain scoring systems, less postoperative hemorrhage rates, less postoperative emesis events, reduced total required doses of pain medication, and more rapid return to normal activity and normal diet, when compared to those treated with fibrin sealant alone or no fibrin sealant.

Approach to Test Hypothesis

Pre-clinical Phase:

Prior to initiating evaluation of the bupivacaine-infused fibrin sealant in patients, evaluating the effect of adding the bupivacaine to the fibrin sealant with regard to adhesion strength and gross time to coagulation will be necessary to ensure that no deleterious effects are inadvertently achieved (Kitajiri). See procedures section below for more specific details regarding pre-clinical testing materials and methods.

Clinical Phase:

The effectiveness of bupivacaine-infused fibrin sealant on reducing postoperative pain and hemorrhage in children undergoing tonsillectomy or adenotonsillectomy will be evaluated. Children undergoing tonsillectomy or adenotonsillectomy at Riley Hospital for Children will be considered for inclusion. Patients included in the study will undergo tonsillectomy or adenotonsillectomy with the coblation device (ArthroCare® Corporation, Austin, TX) and be randomized to one of three experimental arms: 1. topical application of the bupivacaine-infused fibrin sealant to the tonsil fossae and adenoid bed (if adenoidectomy was also performed), or 2. topical application of fibrin sealant alone to the tonsil fossae and adenoid bed (if adenoidectomy was performed), or 3. no topical application with wound bed open to the air (current standard practice at our institution). Meta-analysis have found no clear benefit in local anesthetics alone so a local anesthetic only arm will not be included (Hollis). Patients and parents/guardians will be blinded to their treatment arm as will individuals performing study data analysis. See procedures section below for specific details regarding materials and methods.

Outcome Measures

Primary clinical outcome measures evaluated in each arm of the experiment will include age-appropriate validated pain scale measurement data as well as post-tonsillectomy primary and secondary hemorrhage rates. Secondary outcome measures will include overnight pain medications usage, daily occurrence of emesis, total postoperative days until cessation of all analgesic requirements, total postoperative days until resumption of normal activities, total postoperative days until resumption of normal diet, total analgesic doses required per day (including narcotic dose component if applicable), necessity of contacting ENT doctor on-call, and necessity of contacting the ENT clinic.

Pain Assessment:

For children 1 year of age through 12 years of age, the Parent's Postoperative Pain Measure (PPPM) will be utilized to provide parents with assessment tools for accurately measuring and recording young children's pain levels. The PPPM was developed by Chambers et al. in 1996 and has been independently tested and validated

as a well-established assessment of postoperative pain by parents for young children; this assessment demonstrates high inter-rater reliability and internal consistency and correlates well with validated self-assessment measures in older children (Chambers, Baeyer 2007). No single pain assessment scale among the well-validated and widely used scales in pediatric populations have been demonstrated to be superior to another, but the author of one review article recommends the PPPM specifically for postoperative pain (Tomlinson, Baeyer 2007). This assessment involves parents providing binary answers (0 or 1) to 15 questions and summing all questions (Chambers, Baeyer 2007).

Parents/guardians for all treatment arms will be provided pain recording data sheets as well as pre-addressed pre-stamped envelopes for returning pain recording data sheets to the research facility. Parents/guardians will be encouraged to utilize pain assessments as these will enable them to most accurately assess and adequately treat their child's pain. Pain assessments will be performed three times daily: morning, afternoon, evening. Paperwork and patient information handling is discussed in the privacy section below. Parents/guardians of all treatment arms will be contacted approximately 2 to 3 weeks postoperatively to remind family to return their pain recording data sheets.

Hemorrhage Assessment:

All parents/guardians will be contacted approximately 2 to 3 weeks postoperatively. During this contact, the question of occurrence and timing of postoperative bleeding will be posed. Any bleeding requiring presentation to an emergency department, admission, and/or return to the operating room will be considered significant and recorded with degree of necessary intervention noted; self-limited minimal bleeding (<15mL, 1 tablespoon) or subjective reports of tasting blood without visually observing blood will not be considered significant bleeding. Primary tonsil hemorrhage (occurring <24 hours following surgery) versus secondary tonsil hemorrhage (occurring >24 hours following surgery) will be distinguished in data analysis.

Assessment of Secondary Outcomes:

The pain recording data sheets will include daily assessment of total analgesic doses required for day (including narcotic dose component if applicable). The pain recording data sheets described above will also contain daily "Yes/No" assessments of questions regarding: 1) "Did your child require pain medications during sleeping hours last night?", 2) "Did your child throw up today (include number of times)?", 3) "Did your child resume their normal activity level today?", 4) "Did your child resume their normal diet today?", 5) "Did you need to call ENT MD after business hours?", and 6) "Did you need to call the ENT clinic during the day?". Additionally, pain medicine usage will be evaluated with the following input statements: 1) "Total Doses of narcotic pain medication required in last 24 hours?" and "Total Doses of non-narcotic pain medication required in last 24 hours." This information will be returned simultaneously on the pain recording data sheets in the same pre-addressed pre-stamped envelopes. Parents/guardians will be reminded by phone correspondence approximately 2 to 3 weeks postoperatively to include this data in their pain recording data sheets before mailing them back to researchers.

3.0 Inclusion/Exclusion Criteria

Inclusion

- Age: 1 year old through 12 years of age.
- Weight: 10 kilograms or more.
- Undergoing tonsillectomy or adenotonsillectomy for the following conditions:
 - Chronic Pharyngitis / Recurrent Tonsillitis
 - PAPFA Syndrome
 - Upper Aerodigestive Obstruction Symptoms (sleep disordered breathing, dysphagia deemed secondary to tonsil size, etc)
 - Adenotonsillar Hypertrophy (ATH)
 - Obstructive Sleep Apnea (OSA; clinical diagnosis or by polysomnogram)
 - Chronic/Recurrent Tonsillolithiasis (Tonsil stones)

Exclusion:

- Undergoing additional surgical procedures within 14 days preceding or following the tonsillectomy or adenotonsillectomy.
- Undergoing additional procedures concurrently with tonsillectomy or adenotonsillectomy other than (children receiving supraglottoplasty (SGP) will be excluded):
 - direct laryngoscopy (DL)
 - bronchoscopy (B)
 - nasal endoscopy
 - ear examination under anesthesia (E-EUA) and/or cerumen removal
 - bilateral myringotomy with insertion of ventilation tubes (BMT)
- Tonsillectomy or adenotonsillectomy being performed for concern of malignancy of unknown primary.
- Documented aprotinin allergy.
- Documented allergy to amide local anesthetics (lidocaine, bupivacaine, etc).
- Documented bleeding disorder or chronic anticoagulant use.
- History of chronic pain disorder.
- Chronic use of prescription narcotics or methadone.
- Documented history of substance abuse or illicit drug use.
- Documented history of alcoholism or alcohol abuse.
- Gastrostomy/orogastric/nasogastric tube placement/use.
- Planned intensive care unit (ICU) placement postoperatively.
- Refusal to participate (Jehovah's Witness – Fibrin sealant contains blood product)
- Exclusion at the judgment of the investigator (e.g. ward of court, language barriers, etc.).

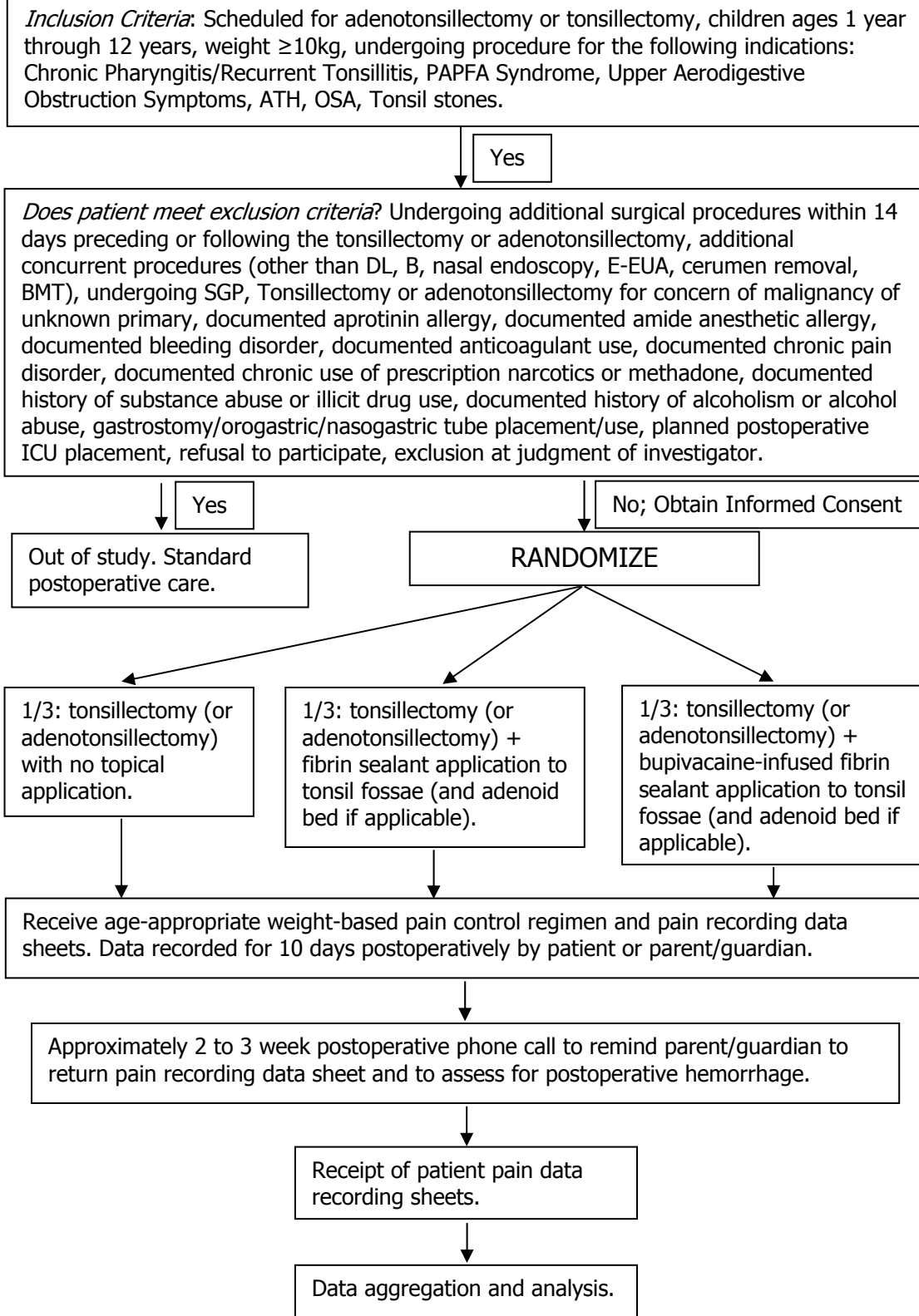
4.0 Enrollment/Randomization

Randomization will occur using an a priori computerized schedule. The computerized schedule will be consulted by the surgeon in the operating room (OR) on the day of surgery to determine into which arm the subject will be placed. Surgeons will not know prior to OR time into which arm the patient will be randomized. Patients or guardians/parents will not be informed into which arm they have been randomized.

All randomizations will occur in the ORs at Riley Hospital for Children.

5.0 Study Procedures

Outline of Research Plan



Preclinical Evaluation

Synthesis of Bupivacaine-infused Fibrin Sealant:

1mL 0.75% bupivacaine solution will be added to EITHER the 4mL Baxter® Health Corporation Tisseel® brand fibrin sealant Duo Set® prefilled dual syringe system OR the 4mL Ethicon® Corporation Evicel® brand fibrin sealant Application Device by injecting 0.5mL bupivacaine solution into each syringe barrel using the technique described in Section 15 or Section 16 below (equivalent products by different vendors). Then bupivacaine-infused sealant will be applied to the wound beds. It is anticipated that this will dilute the fibrin sealant components by 20% while infusing the bupivacaine to a concentration of 0.15% (or 1.5mg per 1 mL). While it might be supposed that reducing the fibrin sealant concentration would lower the adhesion strength, Kitajiri et al. found that the addition of lidocaine actually increased adhesion strength despite prolonging time to coagulation because of the removal of CaCl from the fibrin sealant components (Kitajiri). As the proposed infusion of bupivacaine does not require the removal of the CaCl component, there is not anticipated to be an unduly prolonged coagulation time. In fact, preliminary testing demonstrated no gross difference in time to coagulation with both the unaltered fibrin sealant and the bupivacaine fibrin sealant coagulating within several seconds after application.

Assessing Adhesion Strength:

A uniform aliquot of unaltered fibrin sealant will be utilized to affix the head of a 2.38mm diameter plastic cylinder to a flat plastic sheet. This will be allowed to dry for 3 minutes as per fibrin sealant instruction. Then, a sheering force will be applied in plane with the flat plastic sheet in order to determine the sheering strength in grams/cm² required to dislodge the plastic cylinder. This will be repeated for a total sample size of 10. An identical procedure will be performed to assess the adhesion strength for the bupivacaine-infused fibrin sealant prepared as described above. Again, this will be repeated 10 times. Means between groups will be compared with 2-tailed T-tests.

Clinical Evaluation

Preoperative Management:

As per our routine, the patient will initially be placed under general anesthesia by the anesthesia personnel using intravenous (IV) or inhaled anesthetic and cardiopulmonary monitoring is continued throughout the case. The patient generally receives 1mg/kg dose of IV dexamethasone up to 10 or 20mg (surgeon dependent). No perioperative antibiotics are administered unless the patient has an indication (e.g. artificial heart valve or significant valvular defect). Preoperative antiemetics are not routinely administered. Some patients may undergo airway evaluation with direct laryngoscopy or bronchoscopy and typically receive a half maximum dose (2-3mg/kg) of topical lidocaine sprayed directly onto the supraglottis and vocal folds. If supraglottosty is performed, the patient will not be included in the study as this contributes an additional wound bed in the throat. After the patient is intubated with an oral Ring Adair and Elwyn (RAE) endotracheal tube (ETT) and the ETT is secured in place over the midline lower lip, the patient is draped for tonsillectomy or adenotonsillectomy.

If the patient has been randomized to the bupivacaine-infused fibrin sealant arm or the fibrin sealant alone arm of the study, then the fibrin sealant will be thawed as per

brand instructions. For the bupivacaine-infused fibrin sealant arm of the study, 1mL of 0.75% bupivacaine preservative free solution will be drawn into the fibrin sealant applicator (approximately 0.5mL into each of the two coupled syringes). This mixture will be hand agitated to further facilitate mixing. The total dose of bupivacaine will be 7.5mg (1.5mg bupivacaine per 1mL bupivacaine-infused fibrin sealant). This represents a less than half maximum dose for a 10kg patient so the half maximum dose of topical lidocaine which may have been used during direct laryngoscopy as noted above would be considered safe (total of all local anesthetics would not be over 100% of maximum dose). Either the unaltered fibrin sealant or the bupivacaine-infused fibrin sealant will remain available until needed during the case.

Surgical Technique:

Either a McIvor or Crowe-Davis mouth gag is utilized to provide exposure of the oral cavity and oropharynx and the mouth gag is expanded and suspended from the Mayo stand. If the adenoid bed is to be inspected for removal, the soft palate is palpated to ensure the absence of submucosal clefting and a red rubber catheter is inserted through the nostril and used to retract the soft palate while an angled dental mirror is utilized to inspect the degree of nasopharyngeal obstruction. If the adenoid bed is to be removed with an appropriately-sized adenoid curette, this is generally performed at this time and the nasopharynx is packed with oxymetazoline-soaked sponges. Then, either the left or right tonsil is grasped with a clamp and retracted toward the midline while the Coblator device (ArthroCare® Corporation, Austin, TX), with settings of 7 ablation and 3 coagulation, is used with the other hand to excise the tonsil in a capsular plane between the tonsil and the pharyngeal constrictor muscles laterally. Care is taken to avoid injury to the surrounding musculature and mucosa. The tonsil is amputated and removed from the oral cavity. The same procedure is performed on the remaining tonsil. Areas of bleeding in the tonsil fossae are treated with the coagulation setting of the coblation device to achieve hemostasis.

The adenoid bed, if not previously excised with an appropriately-sized adenoid curette prior to beginning tonsillectomy, is then ablated away utilizing the Coblator device with an ablation setting of 9. Whether curette or Coblator ablation was utilized to remove the adenoid pad, adenoid wound bed hemostasis is subsequently achieved as necessary with the Coblator device using a coagulation setting of 5.

An orogastric tube is passed to suction away gastric and esophageal contents.

Study Interventions:

If patients have been randomized to the fibrin sealant alone application group, then approximately 2mL of fibrin sealant will be applied to each tonsil fossa (enough to cover the entire wound bed) and any remaining fibrin sealant will be applied to the adenoid bed; application will be facilitated using either the 4mL Baxter® Health Corporation Tisseel® brand fibrin sealant Duo Set® prefilled dual syringe system OR the 4mL Ethicon® Corporation Evicel® brand fibrin sealant Application Device. As per fibrin sealant instruction, the product will be allowed to dry for 3 minutes.

If the patients have been randomized to the bupivacaine-infused fibrin sealant group, then approximately 2mL of the bupivacaine-infused fibrin sealant will be applied to each tonsil fossa (approximately 3mg bupivacaine per tonsil fossa) and any remaining bupivacaine-infused fibrin sealant will be applied to the adenoid bed (approximately 1.5mg bupivacaine applied to adenoid bed); as above, application will be facilitated

using the 4mL Baxter® Health Corporation Tisseel® brand fibrin sealant Duo Set® prefilled dual syringe system OR the 4mL Ethicon® Corporation Evicel® brand fibrin sealant Application Device. As per fibrin sealant instruction, the product will be allowed to dry for 3 minutes.

Whether patient has been randomized to receive bupivacaine-infused fibrin sealant, fibrin sealant alone, or no topical application, the mouth gag and red rubber catheter are then removed. All patients are extubated postoperatively in the operating room or occasionally the recovery room.

Postoperative Care:

Cardiopulmonary monitoring is continued for the duration of the hospital stay. Postoperative antibiotics are not routinely administered. If myringotomy with tube placement (BMT) is performed, most patients receive ototopical antibiotics to be used for several days to prevent clogging of the myringotomy tube and reduce postoperative tube otorrhea. BMT pain is negligible in most patients after the first postoperative day; BMT pain is much less on the first postoperative day than the pain caused by tonsillectomy so we do not anticipate that concurrently BMT will confound pain data recording. While in the post-anesthesia care unit (PACU), patients may receive an ice collar to the neck or other general nursing techniques to improve patient comfort.

Acute post-anesthetic nausea may be appropriately treated with an antiemetic in the PACU or hospital ward if the patient is kept for observation. Patients may also receive IV pain medication if necessary during PACU or hospital ward stay, but preference is always given to oral pain medications. Patients are advised to pursue a soft diet as tolerated with emphasis on cold/liquid foods if as needed in the first few days with advancement to regular diet as tolerated. As stated above, parents/guardians will receive pain recording data sheets to be documented three times daily. Patients remaining in the hospital ward for observation will have parent documentation of pain and emesis as though they were at home; where gaps in assessment exist, the medical record will be consulted.

Routine tonsillectomy and adenotonsillectomy postoperative pain regimens include weight-based acetaminophen oral solution (15mg/kg PO Q6H prn pain) or for older children and adults acetaminophen/hydrocodone 7.5mg/325mg/15mL elixir (0.2mL to 0.3mL/kg PO Q6H prn pain) or acetaminophen/hydrocodone tablets (5mg/325mg 1-2 tabs PO Q6H prn pain). Typically, the acetaminophen containing medication is alternated with ibuprofen oral solution (10mg/kg PO Q6H prn pain) or ibuprofen tablets (400mg or 600mg, dependent upon weight, PO Q6H prn pain) so the patient may receive a pain medication as frequently as every 3 hours if needed. Patients with liver or kidney pathology or history of gastric ulcers or NSAID intolerance may be provided alternate pain regimens. Parents/guardians are typically advised to schedule pain medications the first postoperative day and to set an alarm for pain medication overnight in order to prevent falling behind on pain control.

All patients and parents/guardians will receive standardized postoperative care instructions with regard to diet, pain control regimen, wound changes, bleeding, and journal recording.

6.0 Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

Adverse events (AEs) will be reported to the Internal Review Board (IRB).

For AEs requiring prompt reporting, the appropriate PROMPT REPORTING FORM will be used. These will be submitted to the IU Human Subjects Office at (317) 278-8289.

For AEs not requiring prompt report, the information will be included in the continuing review forms.

Tonsil hemorrhage or need to return to the OR to control tonsil hemorrhage are not considered AEs for this study.

Safety Monitoring

At all times we are available for questions and concerns, and should at any time a subject in any arm of the study experience a complication or adverse event, we will intervene as appropriate. A theoretical risk exists of allergic reaction to the aprotinin component of the fibrin sealant and thus patients with known aprotinin allergy will be excluded from this study. As the fibrin sealant is synthesized from human plasma, a theoretical risk of viral particle transmission exists (Tisseel® Prescriber Information Document, Dhillon), but no confirmed cases of HIV or Hepatitis C transmission have occurred (Joch). Prior studies documenting use of fibrin sealant in the setting of adenotonsillectomy or tonsillectomy have reported no adverse events (Dhillon, Gross, Kitajiri, Moralee, Nam, Segal, Stevens, Stoeckli, Vaiman 2003, Vaiman 2006, Vaiman 2007, Jo, Park). Similarly, studies cited above documenting the topical use of bupivacaine in the setting of tonsillectomy or adenotonsillectomy have reported no significant adverse events or complications (Haksever, Kaygusuz, Ozmen).

If a patient in any arm clinically deteriorates or manifests one of the exclusion criteria postoperatively, we will treat them as needed. If any significant negative trend of adverse events related to the study intervention is noted, we will immediately postpone or terminate the study and notify the IRB of our findings.

7.0 Study Withdrawal/Discontinuation

The subject may choose to leave the study at any time, whether by declaring he or she is withdrawing or by failing to return the pain recording data sheets. The subject may also be withdrawn from the study, if in the opinion of the investigator, continued participation would be detrimental for the care or health of the subject. Leaving the study will not result in any penalty or loss of benefits. The decision whether or not to participate in this study will not affect the subject's current or future relations with Riley Hospital, Indiana University School of Medicine, nor Indiana University Health Physicians. Subjects who withdraw from the study will not continue to be followed for the purposes of this study. Any viable data obtained during the study on withdrawn subjects will be kept though as part of the study and included in the final results. A referral to their withdrawal will be mentioned.

8.0 Statistical Considerations

A prior study demonstrated an average pain score of 7.2 on the first postoperative day for tonsillectomy without post-operative fibrin sealant application or local anesthetic injection with a standard deviation of 3, thus with a sample size of 44 per treatment arm, this study will have 80% power to detect a 25% difference in pain scores between two treatment arms, assuming two-sided tests each conducted at a 5% significance level (Segal). Repeated measures analysis of variance (ANOVA) will be utilized to analyze pain score differences between groups and over time; distributional assumptions for the ANOVA will be checked, and nonparametric analyses will be performed if the assumptions are not satisfied. For hemorrhage rates, the low incidence in the general population makes power-scaling impractical and thus chi-square tests will be utilized to make comparisons between arms. For postoperative emesis frequency rate and necessity to contact the clinic or the physician on call, analysis of arms will likely proceed by Kruskal-Wallis or Wilcoxon Rank Sum tests. Days until narcotic discontinuation, days until analgesic discontinuation, days until resumption of normal activities, and days until resumption of normal diet will be analyzed between treatment arms likely using log-rank survival analysis and Kaplan-Meier curves.

9.0 Privacy/Confidentiality Issues

Efforts will be made to keep all personal information confidential. Subject identity will be excluded in published reports and databases in which results may be stored.

- To assure confidentiality, the initial data will be entered into a database located in a password-protected desktop computer. Once data is entered into the database, paper forms will be scanned electronically and stored as .PDF files on the abovementioned desktop computer prior to being placed in appropriate HIPAA compliant shredder bins for disposal. All study information will be located in an area with limited public access.
- Privacy will be ensured by confirming with the patient or parents/guardians that they are in a place where they feel comfortable discussing their or their child's medical management before proceeding further with the study.
- Any publication resulting from this investigation will protect the patient's privacy by excluding any identifier.

10.0 Follow-up and Record Retention

Enrollment will continue until 44 subjects per treatment arm have had their postoperative pain recording data sheets returned (see statistical section above). Should a patient be enrolled but data not be returned for analysis, they will be considered withdrawn from the study and another enrollment will be required to achieve final sample size for adequate statistical power.

Data will be retained before discarding for a minimum of 7 years for health data, per Indiana State law. When data will be discarded: any remaining paper documents will be placed in HIPAA compliant shredding bins for disposal and there will be a permanent deletion of the data from the desktop.

11.0 Anticipated Results, Potential Issues, Alternative Approaches

A reduction in the postoperative validated pain scores during the first 4 to 5 postoperative days is anticipated. As mentioned above, prior studies have demonstrated the maintenance of fibrin sealant on the tonsillectomy site for at least this long and studies of local anesthetic release dynamics from fibrin sealant have suggested release for at least 4 days or more with release duration dependent on fibrin/thrombin concentrations (Itokazu, Spicer). Prior studies have not consistently reported a reduction in post-tonsillectomy hemorrhage and uncertainty remains in whether this study will find a reduction.

With regard to secondary outcome measures, reduced postoperative emesis has been reported in association with fibrin sealant application following tonsillectomy and we anticipate similar reduction in our study (Gross). We also anticipate reduced total days to cessation of analgesic usage, reduced total days to cessation of narcotic usage, reduced total days to return to normal diet, and reduced total days to return to normal activity when bupivacaine-infused fibrin sealant is applied following tonsillectomy or adenotonsillectomy compared to fibrin sealant alone or no topical application.

One concern of this study is the possibility of poor compliance on the part of parents/guardians in recording their pain scores consistently or failure to return their pain recording data sheets as requested. Segal in 2007 demonstrated an approximately 60% return rate for pain journal materials by included patients (Segal). In order to improve compliance, the pain recording data sheet will be composed as simply as possible and with patient/parent-friendly language. Pre-addressed pre-stamped envelopes will also be provided. Clinic nurses will conduct phone calls approximately 2 to 3 weeks postoperatively to remind parents/guardians to complete and return their pain recording data sheets.

12.0 Grant Targets

American Academy of Otolaryngology – Head & Neck Surgery Foundation (AAO-HNSF) Resident Research Award—Open to any AAO-HNS member in good standing who is a resident in an accredited otolaryngology-head and neck surgery training program in the U.S. or Canada. One year, any topic, non-renewable, \$10,000 maximum total costs, up to eight available annually.

AAO-HNSF Resident Research Grant sponsored by Cook Medical- Open to any AAO-HNS member in good standing who is a resident in an accredited otolaryngology-head and neck surgery training program in the U.S. or Canada. Proposed projects may be related to paranasal sinus disease, salivary gland disease, sleep medicine, voice therapy, airway, ultrasound and tissue engineering. One year, non-renewable, \$10,000.

Indiana Clinical and Translational Sciences Institute Research Invention and Scientific Commercialization Program (CTSI RISC) – Projects with immediate potential to commercialize inventions, technologies or intellectual property. Grants open to IU faculty applicants, requires IURTC endorsement letter. \$25,000 maximum, one-year project.

Baxter® Healthcare Corporation BioScience Research Grant – Open to any clinical researcher. Proposed projects are reviewed quarterly (Submission due August 31, 2014). No listed duration restriction, \$5,000 to \$125,000 maximum cost.

13.0 Contacts

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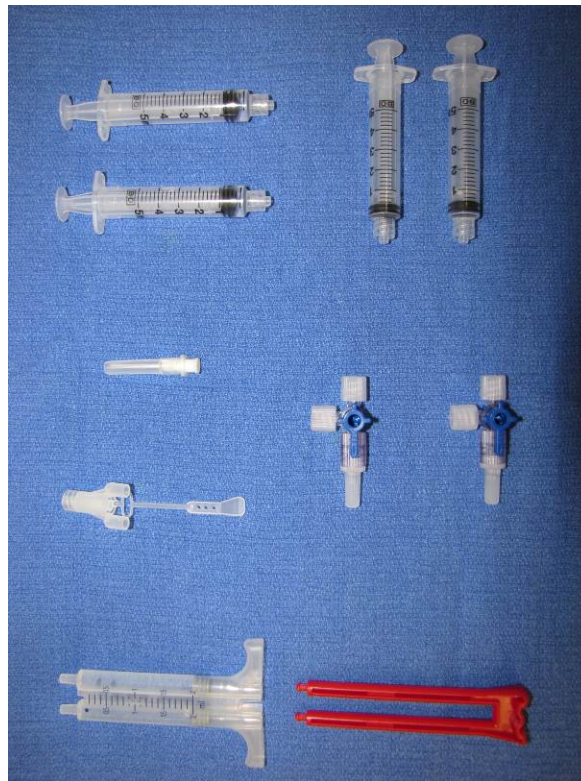
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15.0 Infusing the Tisseel® Duo Set® System with Bupivacaine

The following figures and descriptions will be provided to personnel preparing the 0.75% bupivacaine-infused fibrin sealant for use in this study:

Step 1: Material Acquisition & Arrangement:

The 4mL Baxter® Health Corporation Tisseel® brand fibrin sealant Duo Set® prefilled dual syringe system must first be thawed per included instructions and arranged on the sterile field including the dual syringe barrels, the red plunger, the joining Y-connector piece with fastening strap, and the application cannula. Two empty sterile 5 mL syringes are also arranged on the sterile field. Two 5 mL sterile syringes containing 0.5mL each of 0.75% bupivacaine solution (*with all air bubbles evacuated*) are placed on the sterile field with the other supplies. Finally, two sterile 4-way stopcocks are arranged on the sterile field. The sterile syringes and stopcocks are contained in the anesthesia storage within each OR. The 0.75% bupivacaine solution will be kept at appropriate temperature in the OR or obtained from the OR pharmacy.



Step 2: Inserting the Plunger Unilaterally.

The red plunger should be oriented perpendicularly (90°) to the plane of the face of the dual syringe so that only a single syringe barrel plunger head is engaged. Eject all air bubbles from the dual syringe barrel.



Step 3: Attaching the 0.75% Bupivacaine Syringe to the Duo Set® Syringe Barrel

The 2 protective caps should be unscrewed from the female ends of one of the 4-way stop-cocks while the larger male end cap of the 4-way stop-cock should remain in place. One of the two 5 mL syringes prefilled with 0.5mL 0.75% bupivacaine solution should be firmly screwed to one female end of the 4-way stop-cock. The "off" valve of the 4-way stop-cock should be oriented to point toward the large still capped male end. The syringe barrel male tip of the side with the single red plunger shaft inserted should be pushed firmly (does not screw) into the available female end of the 4-way stop-cock.



Step 4: Injecting the Fibrin Sealant Component Syringe Barrel Contents into the 5 mL Syringe Containing 0.5mL of 0.75% Bupivacaine Solution.

While supporting the 4-way stop-cock's attachment to the Duo Set[®] syringe barrel with one hand, the red plunger is depressed with the other hand. This forces the fibrin sealant component through the 4-way stop-cock into the 5 mL syringe containing 0.75% bupivacaine solution. **NOTE:** Failure to manually support the connection between the 4-way stop-cock and the Duo Set[®] syringe male end could result in spillage of the fibrin sealant contents as this connection is not affixed by screwing the attachments. The cost per fibrin sealant kit is ~\$200.



Step 5: Mixing the Fibrin Sealant Component with the 0.75% Bupivacaine Solution.

Detach the male end of the Duo Set[®] syringe from the female end of the 4-way stop-cock (some minute spillage of contents may occur with this). Then screw on one of the empty 5 mL syringes to the female end of the 4-way stop-cock. Again, ensure the "off" valve of the 4-way stop-cock is oriented to point toward the large still-capped male end. Alternatingly compress the plungers of each of the 5 mL syringes attached to the 4-way stop-cock to force fluid contents from one 5 mL syringe to the other. Continue this process for 30 seconds. This will agitate and mix the fibrin sealant component with the 0.75% bupivacaine.



Step 6: Injecting the Fibrin Sealant Bupivacaine Mixture Back Into the Duo Set® Syringe.

Compress all of the fibrin sealant 0.75% bupivacaine mixture into a single 5 mL syringe on one side of the 4-way stop-cock by completely depressing the opposite 5 mL syringe plunger. Detach the empty 5 mL syringe and discard from sterile field. Eject any air bubbles from the 5 mL syringe and the 4-way stopcock. Firmly reinsert the male end of the *empty* Duo Set® syringe barrel to the free female end of the 4-way stop-cock. *Slowly* depress the 5 mL syringe barrel while supporting the connection between the 4-way stop-cock and the Duo Set® syringe barrel (failure to do so could result in spillage of contents, ~\$200). Entirely discard the now empty 5 mL syringe and 4-way stop-cock from the sterile field. This side of the Duo Set® syringe barrel will now contain 2.5mL of fibrin sealant component and 0.75% bupivacaine mixture and the grey plunger gasket will have been pushed past the 2mL hash mark. **NOTE:** It is essential the used 5mL syringes and 4-way stop-cock from steps 2-5 be entirely discarded from the sterile field at this time as inadvertently prematurely mixing contents between the Duo Set® syringe barrels will activate the fibrin sealant.

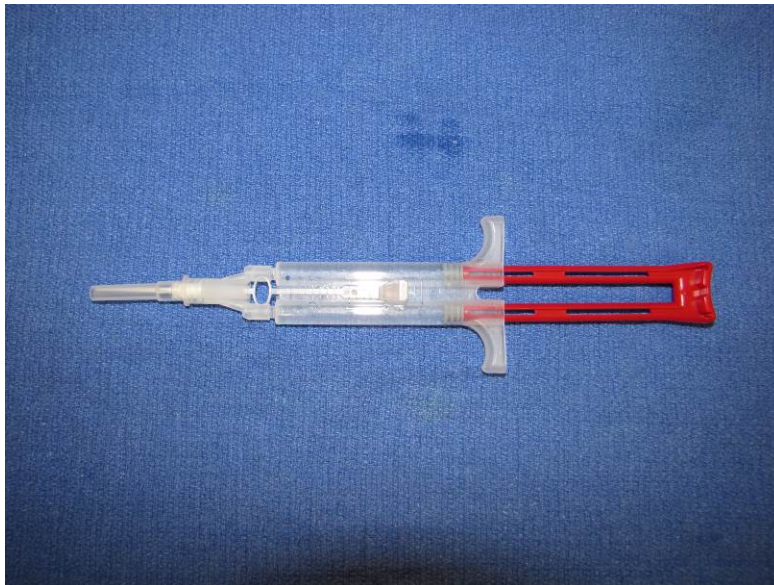
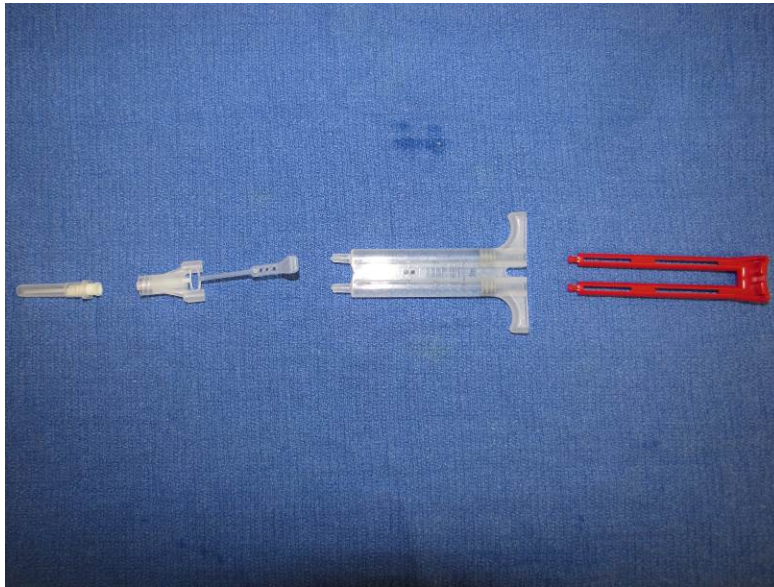


Step 7: Steps 2-6 are Now Repeated for the Contralateral Duo Set® Syringe Barrel.

At this time, the same steps above are repeated using the fresh *unused* 5 mL syringe containing 0.5mL of 0.75% bupivacaine solution, the fresh *unused* 4-way stop-cock, and the fresh *unused* empty 5 mL syringe. Again, the used leftover 5 mL syringes and the 4-way stop-cock should be discarded.

Step 8: Arranging the Bupivacaine-infused Duo Set® System for Use.

Each barrel of the Duo Set® system now contains 2.5mL of 0.15% bupivacaine-infused fibrin sealant component and should have its gray plunger gasket positioned beyond the 2 mL hash mark as 0.5mL of 0.75% bupivacaine has been added to each barrel. This results in 1.5mg/mL concentration of bupivacaine. The red plunger can be inserted parallel to the plane of the Duo Set® syringe so each plunger head engages the gray plunger gasket of its respective syringe barrel. The plunger may be depressed to remove any air bubbles in the Duo Set® syringe barrels. The joining Y-connector piece's female ends are aligned with the male ends of the Duo Set® syringe barrels and attached. The fastening strap male piece is inserted into one of the holes on the face of the Duo Set® syringe. Finally, the application cannula is screwed onto the end of the joining Y-connector.



Step 9: Application of Bupivacaine-infused Fibrin Sealant to the Wound Beds.

The applicator tip is placed over the tonsil fossa and an even layer of bupivacaine-infused fibrin sealant is applied at a steady rate by plunger depression. Approximately 2 mL of the bupivacaine-infused fibrin sealant (3mg bupivacaine) should be applied to a single tonsil fossa in order to evenly and entirely coat the exposed muscular wound bed. The application cannula should be removed and discarded if it becomes clogged and a fresh application cannula should be screwed on to complete application as necessary. Any remaining bupivacaine-infused fibrin sealant can be applied to the adenoidectomy wound bed as able.

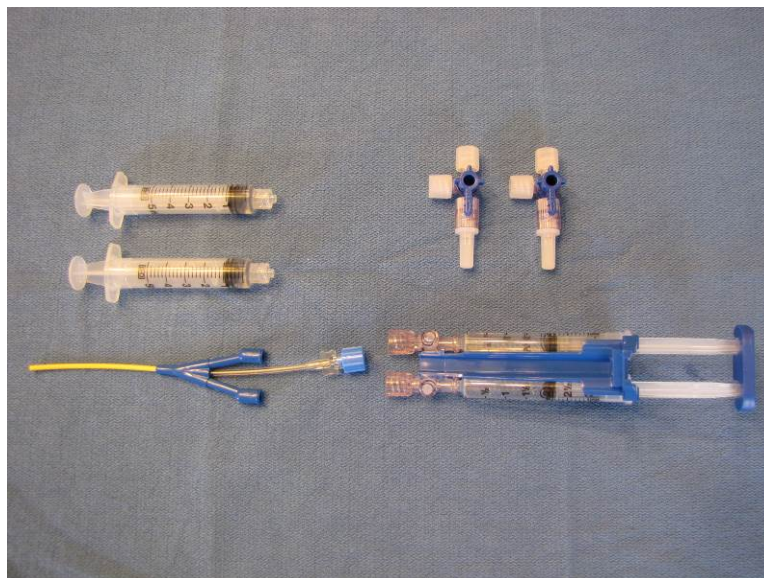


16.0 Infusing the Evicel® Application Device with Bupivacaine

The following figures and descriptions will be provided to personnel preparing the 0.75% bupivacaine-infused fibrin sealant for use in this study:

Step 1: Material Acquisition & Arrangement:

The 4mL Ethicon® Corporation Evicel® brand fibrin sealant Application Device must first be pre-filled with 2mL of the BAC2 (fibrinogen) solution in one syringe barrel and 2mL of the thrombin solution in the other syringe barrel per included instructions. The Application Device contents should then be arranged on the sterile field including the dual syringe barrel applicator and the joining Y-connector with attached cannula. Two 5 mL sterile syringes containing 0.5mL each of 0.75% bupivacaine solution (*with all air bubbles evacuated*) are placed on the sterile field with the other supplies. Finally, two sterile 4-way stop-cocks are arranged on the sterile field. The sterile syringes and stopcocks are contained in the anesthesia storage within each OR. The 0.75% bupivacaine solution will be kept at appropriate temperature in the OR or obtained from the OR pharmacy.



Step 2: Attaching the 0.75% Bupivacaine Syringes to the Application Device

The 2 protective caps should be unscrewed from the female ends of one of the 4-way stop-cocks while the larger male end cap of the 4-way stop-cock should remain in place. One of the two 5 mL syringes prefilled with 0.5mL 0.75% bupivacaine solution should be firmly screwed to one female end of one the 4-way stop-cocks; the other 5 mL syringe prefilled with 0.5mL 0.75% bupivacaine solution should be firmly screwed to the other 4-way stop-cock's female end. The "off" valve of the 4-way stop-cocks should be oriented to point toward the large still capped male end. The free female ends of the two stop-cocks should be firmly screwed onto the free ends of the Application Device's syringe barrels as shown below.



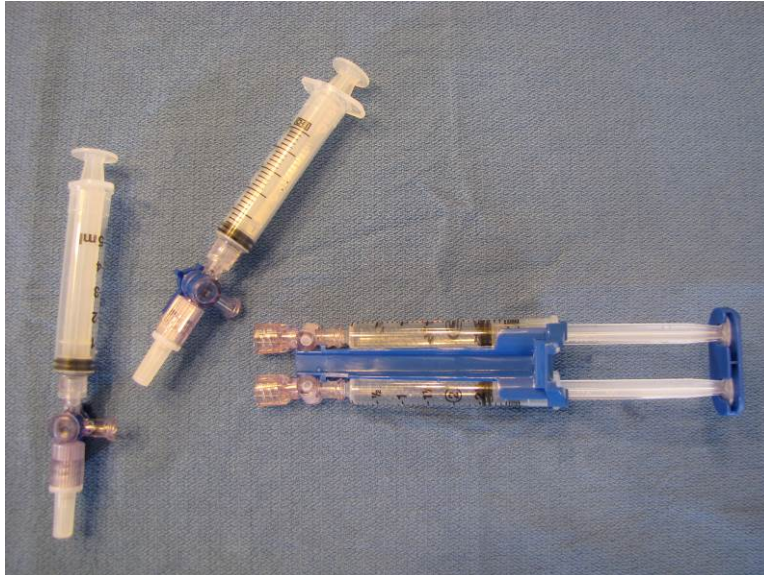
Step 3: Mixing the Fibrin Sealant Component with the 0.75% Bupivacaine Solution.

After the stop-cocks are firmly affixed to the Application Device's two syringes containing fibrin sealant components and the stop-cocks' other female ends are each attached to the two 5mL syringes containing 0.5mL of 0.75% bupivacaine solution, the syringe barrel plungers are alternately depressed to force the fibrin sealant components to mix with bupivacaine solution through their respective stop-cocks. Alternatingly compress the plungers of each of the 5 mL syringes attached to the 4-way stop-cocks with the plungers of the Application Device to force fluid contents from the application device to the 5mL syringes and back again. Continue this process for 30 seconds. This will agitate and mix the fibrin sealant component with the 0.75% bupivacaine. Complete this step by depressing the 5mL syringe plungers to push the newly mixed bupivacaine infused fibrin sealant components back into the Application Device.



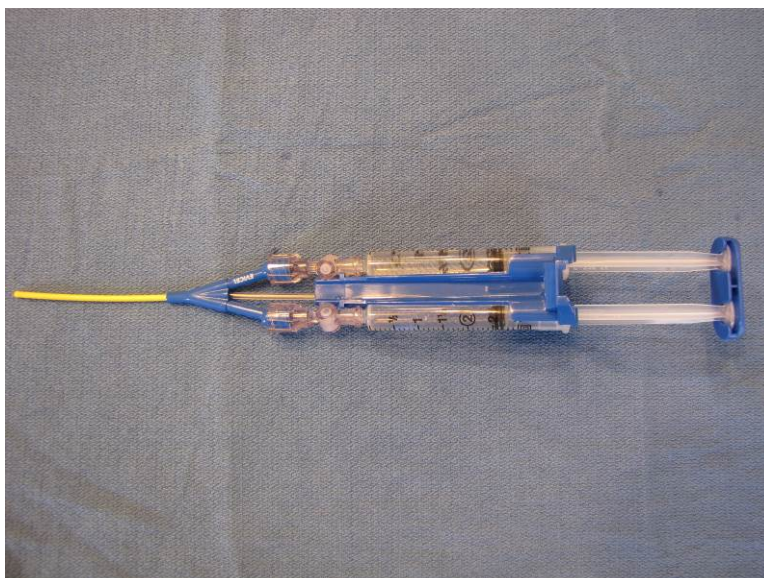
Step 4: Removing the Stop-cocks and Empty 5mL Syringes From the Application Device.

After compress all of the bupivacaine-infused fibrin sealant components back into the Application Device, detach the empty 5 mL syringes and stop-cocks and discard from sterile field.



Step 5: Arranging the Bupivacaine-infused Application Device for Use.

Each barrel of the Application Device now contains 2.5mL of 0.15% bupivacaine-infused fibrin sealant component and should have its black plunger gasket positioned near the 2.5mL hash mark as 0.5mL of 0.75% bupivacaine has been added to each barrel. This results in 1.5mg/mL concentration of bupivacaine. The plungers of the Application Device may be depressed carefully to remove any air bubbles in the syringe barrels. The joining Y-connector piece's female ends are aligned with the male ends of the Application Device syringe barrels and attached.



Step 6: Application of Bupivacaine-infused Fibrin Sealant to the Wound Beds.

The applicator tip is placed over the tonsil fossa and an even layer of bupivacaine-infused fibrin sealant is applied at a steady rate by plunger depression. Approximately 2 mL of the bupivacaine-infused fibrin sealant (3mg bupivacaine) should be applied to a single tonsil fossa in order to evenly and entirely coat the exposed muscular wound bed. The Y-piece/application cannula should be removed and discarded if it becomes clogged and a fresh application cannula should be screwed on to complete application as necessary. Any remaining bupivacaine-infused fibrin sealant can be applied to the adenoidectomy wound bed as able.

